REMARKS

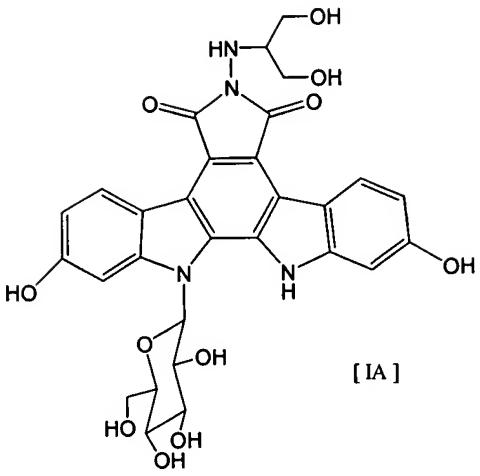
Entry of the foregoing amendments and favorable consideration of the subject application is respectfully requested in view of the following comments.

Claims 1-23 and 34-35 are currently pending in this application. Claims 1, 11, 14, and 34 have been amended and claims 2-10, 13, 15-23 and 35 have been cancelled. Accordingly, claims 1, 11, 12, 14 and 34 are herewith presented for examination.

Claims 1, 14 and 34 have been amended to more particularly recite the invention as a combination of the specific compound of formula IA and a specified list of antitumor agents which combination exhibits a synergistic effect in the treatment of cancer.

Specifically, claim 1 now recites a combined preparation for simultaneous, separate, or sequential administration in the treatment of cancer, comprising two separate preparations:

(a) a first preparation comprising, in combination with a pharmaceutically acceptable carrier or diluent, a compound of formula IA:



[IA]

or a pharmaceutically acceptable salt thereof; and

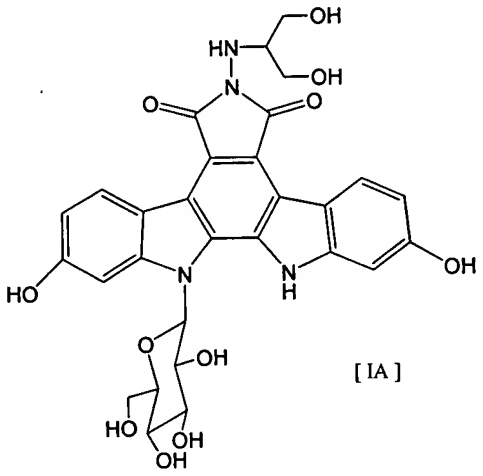
(b) a second preparation comprising, in combination with a pharmaceutically acceptable carrier or diluent, at least one antitumor agent selected from the group consisting of 5-fluorouracil, doxorubicin, etoposide, cisplatin, carboplatin, irinotecan, topotecan, and campthotecin, or a pharmaceutically acceptable salt thereof (wherein, if said preparation contains 5-fluorouracil, it may further contain leucovorin or may be combined with a separate leucovorin preparation).

Accordingly, claim 1 has been restricted to the compound of formula IA, which is the form of general formula I originally recited in claim 10, in combination with at least one antitumor agent selected from the listed group of eight such agents culled from the original recitation of claim 1, with the added proviso, originally recited in now cancelled claim 2, that, if the antitumor agent 5-fluorouracil is present, the preparation may further contain leucovorin or be combined with a separate

leucovorin preparation.

Similarly, claim 14 has been amended to recite a method for cancer treatment comprising simultaneously, separately or sequentially administering to a cancer patient:

(a) a therapeutically effective amount of a compound of formula IA:



[IA]

or a pharmaceutically acceptable salt thereof; and

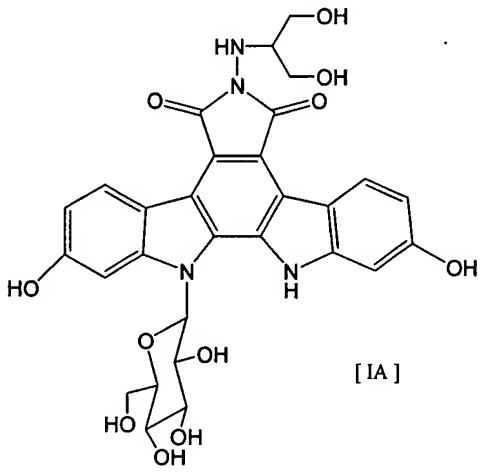
(b) a therapeutically effective amount of at least one antitumor agent selected from the group consisting of 5-fluorouracil, doxorubicin, etoposide, cisplatin, carboplatin, irinotecan, topotecan, and campthotecin, or a pharmaceutically acceptable salt thereof (wherein, if the compound of formula IA is combined with 5-fluorouracil, leucovorin may be further combined.

Thus, amended claim 14 has also been restricted to the compound of formula IA, which is the form of general formula I originally recited in claim 23, in combination with at least one

antitumor agent selected from the listed group of eight such agents culled from the original recitation of claim 14, with the added proviso, originally recited in now cancelled claim 15, that, if the compound of formula IA is combined with the antitumor agent 5-fluorouracil, leucovorin may be further combined.

Furthermore, claim 34 has been amended to recite a pharmaceutical composition comprising, in combination with a pharmaceutically acceptable carrier or diluent:

(a) a therapeutically effective amount of a compound of formula IA:



[IA]

or a pharmaceutically acceptable salt thereof; and

(b) a therapeutically effective amount of at least one antitumor agent selected from the group consisting of 5-fluorouracil, doxorubicin, etoposide, cisplatin, carboplatin, irinotecan, topotecan, and campthotecin, or a pharmaceutically acceptable salt thereof (wherein, if said composition contains 5-

fluorouracil, it may further contain leucovorin or may be combined with a separate leucovorin preparation).

Thus, amended claim 34 has also been restricted to the compound of formula IA, which is the form of general formula I originally recited in claim 23, in combination with at least one antitumor agent selected from the listed group of eight such agents culled from the original recitation of claim 34, with the added proviso, originally recited in now cancelled claim 35, that, if the composition contains 5-fluorouracil, it may further contain leucovorin or may be combined with a separate leucovorin preparation.

Claim 11 has been amended to change its dependency from now cancelled claim 10 to herein amended claim 1.

In view of the foregoing, Applicants respectfully submit that no new matter has been added by the amendments herein, that these amendments are properly enterable at this time, and that the application is now in condition for allowance.

Claim Objections

The examiner has objected to claim 1 as lacking the word "or" at the end of the 4th line from the bottom of the second page of claim 1.

Applicants respectfully submit that the foregoing amendment of claim 1 has resolved this objection by cancellation of that portion of the claim language to which the objection refers.

Double Patenting

Claims 1-23 and 34-35 have been rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 of Kojiri, et al., (U.S. Patent No. 5,922,860) in view of Fukuda, et al. ("Synergism between Cisplatin and Topoisomerase I inhibitors, NB-506 and SN-38 in Human Small Cell Lung Cancer Cells", Cancer Research, 56, 789-93, 2/15/1996). The office action states:

> "The claims of the instant application are drawn to combinations of an indolocarbazole of formula I and an additional anticancer agent, such as cisplatin.
>
> Kojiri et al. teach that compounds having the same formula as those of formula Ia of the instant application and their use as antitumor agents. What is not taught is the combinations with additional anticancer agents.
>
> Fukuda et al. disclose synergistic combinations of NB-506 and cisplatin (see abstract-discussion on page 791). Fukuda et al. state that the combination of cisplatin and a topoisomerase I inhibitor has a very interesting strategy for cancer chemotherapy (discussion). What is not taught is the specific compound of formula Ia.
>
> It would have been obvious to one of ordinary skill in the art at the time of the invention to use the topoisomerase I inhibitors of Kojiri et al. in combination with cisplatin with these references before them. Fukuda et al. discuss the potential for synergism in cancer therapy when using cisplatin and a topoisomerase I inhibitor. Morover, it is noted that the compounds of formula Ia are very structurally similar to NB-506 us in Fukuda et al. It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. The idea of combining them flows logically from their having been

individually taught in the prior art. ***In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).*** (Claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be prima facie obvious). See also ***In re Crockett, 279 F.2d 274, 126 USPQ 186 (CCPA 1960)*** (Claims directed to a method and material for treating cast iron using a mixture comprising calcium carbide and magnesium oxide were held unpatentable over prior art disclosures that the aforementioned components individually promote the formation of a nodular structure in cast iron.); and ***Ex parte Quadranti, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992)*** (mixture of two known herbicides held prima facie obvious). Thus it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the art disclosed indolocarbazole of Kojiri et al. with another antitumor agent, especially in light of the synergistic effects shown by Fukuda et al. One would have been motivated to combine these agents to form a new composition which would be used for the very same purpose, as an antitumor agent. Moreover, it is noted that the KSR decision forecloses the decision that teaching/suggestion/motivation is required in making an obviousness rejection."

With regard to the now cancelled claims 2-10, 13, 15-23 and 35, Applicants respectfully submit that the present rejection is now moot.

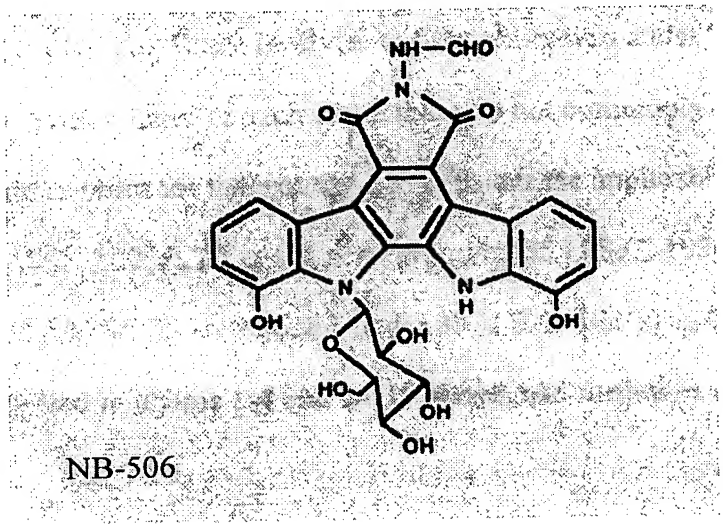
As to amended claims 1, 11-12, 14 and 34, Applicants respectfully traverse the rejection because the prima *facie case* of obviousness has not been established.

According to MPEP §804, an obviousness-type double patenting rejection is "analogous to [a failure to meet] the nonobviousness requirement of 35 U.S.C. 103" citing *In re Braithwaite*, 379 F.2d 594, 154 USPQ 29 (CCPA 1967). "Therefore, the analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. 103 obviousness

determination. In re Braat, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985)."

Considering the references cited by the examiner, Applicants point out that claims 1 and 2 of Kojiri, et al., are directed to the indolocarbazole derivative *per se*, not to any combination of that derivative with other antitumor agents. There is no teaching or suggestion in Kojiri, et al., to any combination of the indolocarbazole derivative with any other active agent.

In contrast, Fukuda, et al. is specifically limited to a combination of the indolocarbazole 6-*N*-formylamino-12,13-dihydro-1,11-dihydroxy-13-(β-D-glucopyranosyl)-5*H*-indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7(6*H*)-dione (NB-506):



NB-506

The reference specifically notes "The indolocarbazole structure of NB-506 is unique among potent topoisomerase inhibitors" and, as such, the reference is limited to that structure and cannot be

said to teach or suggest the structure of Applicants' formula IA as recited in the claims as amended.

Furthermore, Fukuda, et al., is also specifically directed to the combination of NB-506 with cisplatin (CDDP) and camptothecin (CPT-11) and an active metabolite of CPT, SN-38. There is no teaching in the reference of a combination of the indolocarbazole of Applicants' formula IA with an antitumor agent selected from the group consisting of 5-fluorouracil, doxorubicin, etoposide, cisplatin, carboplatin, irinotecan, topotecan and campthotecin, with the possible inclusion, in accordance with the proviso of 5-fluorouracil being present, of leucovorin.

As such, the study presented by Fukuda, et al., demonstrates synergistic effect of cisplatin (CDDP) combined only with CPT-11, SN-38, an active metabolite of CPT-11 and NB-506, while noting that combinations do not always enhance antitumor effect: "However, CPT-11 did not always enhance the antitumor effect of CDDP significantly in mice *in vivo* (25, 26)." (Page 791, lines 22-24). Furthermore, Fukuda, et al., only guesses that "CDDP and topoisomerase I inhibitor combinations have synergistic effects." (Page 791, lines 26-28). Applicants respectfully submit that a "guess" hardly rises to the level of a suggestion much less a teaching.

Applicants further point out that Fukuda, et al., only disclose the indolocarbazole NB-506 in combination with CDDP and

CPT-11. Furthermore, the fact that Kojiri, et al., teach an indolpyrrolocarbazole derivative including the compound IA as being a useful antitumor agent does not imply an expectation of suitability in combination with or as exhibiting a synergistic effect when combined with other antitumor agents.

As is very clear, the chemical structures of NB-506 and formula IA are very different. NB-506 has a moiety of -NH-CHO whereas the compound of formula IA has a moiety of -NH-$CH(CH_2OH)_2$. Furthermore, the two OH groups of NB-506 are located at the 1 and 11 positions while those of formula IA are at the 2 and 10 positions. Given these differences in structure, it would not be expected that the properties and reactivity of NB-506 would be readily attributable to the compound of formula IA. In fact, the chemical and structural differences between NB-506 and the compound of formula IA would lead one to expect different properties and reactivity on the part of formula IA than that shown by NB-506 from the teaching of Fukuda, et al., particularly in view of the uncertainty expressed by Fukuda, et al.

Accordingly, Applicants respectfully submit that in view of such differences, one of ordinary skill in the art would not have expected the specific compound of formula IA to exhibit a synergistic effect in combination with other types of anticancer agents in the manner recited in the claims as amended herein.

Finally, Applicants note that a rejection based on nonstatutory double patenting is based on a judicially created

doctrine grounded in the public policy so as to prevent the unjustified or improper timewise extension of the right to exclude granted by a patent (MPEP §805(II)(B)) The claims of Kojiri, et al. specifically recite "A compound of the general formula … or a pharmaceutically acceptable salt thereof." The claims of Kojiri, et al., do not include any other compound, composition or element other than the specific indolocarbazole recited therein.

In contrast, the present claims, as amended herein, recite, in the case of claim 1, "a combined preparation … comprising two separate preparations …" where one preparation is the indolocarbazole and the second preparation comprises at least one antitumor agent selected from the listed group. Claim 14 recites "a method for cancer treatment comprising … administering to a cancer patient: (a) a therapeutically effective amount of …" the indolocarbazole and "(b) a therapeutically effective amount of at least one antitumor agent selected from the group …". Claim 34 recites "a pharmaceutical composition comprising … (a) a therapeutically effective amount of …" the indolocarbazole and "(b) a therapeutically effective amount of at least one antitumor agent selected from the group …". In each instance, the indolocarbazole is combined with an additional antitumor agent which is at least on of the group consisting of 5-fluorouracil, doxorubicin, etoposide, cisplatin, carboplatin, irinotecan, topotecan, and campthotecin, or a pharmaceutically acceptable

salt thereof. That additional antitumor agent is required to be present as indicated by the use of the combining term "and" in the claims. Without that at least one additional antitumor agent, the present invention does not exist.

Applicants respectfully submit that since the present claims, as amended positively require an additional element that is neither disclosed nor suggested by the Kojiri, et al., reference, nor is required by claims 1 and 2 of the Kojiri, et al., reference, the present claims, as herein amended, are more limiting than the claims of Kojiri, et al., and cannot be seen as extending the right to exclude one from making and/or using the invention that is defined by the claims of Kojiri, et al., i.e., the indolocarbazole derivative by itself.

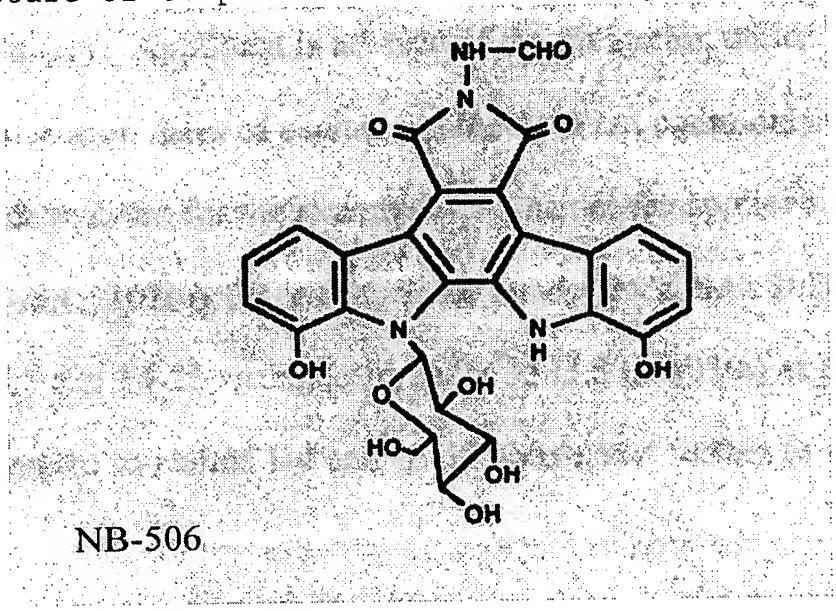
In view of the foregoing, Applicants respectfully submit that the claims of the present invention as amended herein are in the nature of an improvement over the invention of Kojiri, et al., and neither exclude one from making or using the invention of Kojiri, et al, nor extend that right to exclude. Accordingly, Applicants respectfully submit that the basis for the rejection on the ground of nonstatutory obviousness-type double patenting is without support and should be withdrawn.

Claim Rejections - 35 USC §102

Claims 1-4 and 14-17 have been rejected under 35 U.S.C. 102(b) as being anticipated by Fukuda et al. ("Synergism between

Cisplatin and Topoisomerase I inhibitors, NB-506 and SN-38 in Human Small Cell Lung Cancer Cells", Cancer Research, 56, 789-93, 2/15/1996). The office action states:

> "Fukuda et al. disclose synergistic combinations of NB-506 and cisplatin (see abstract-discussion on page 791). Fukuda et al. state that the combination of cisplatin and a topoisomerase I inhibitor is a very interesting strategy for cancer chemotherapy. It is noted that the compounds of the instant application are topoisomerase I inhibitors, as is compounds NB-506. NB-506 is seen to meet the limitations of formula I, and is depicted below as set forth in Kanzawa et al. ("Anti-tumor activities of a new Indolocarbazole Substance", Cancer Research, 55, pp. 2806-13, 7/1/1995). Kanzawa is only being cited to show the structure of compound NB-506 as used by Fukuda et al.



NB-506

"

With regard to claims 2-4 and 15-17, Applicants respectfully submit that the present rejection has been rendered moot by the cancellation of those claims.

As to claims 1 and 14, as amended herein, Applicants respectfully traverse the rejection on the ground that the

reference does not teach each and every claimed limitation of the amended claims.

The Federal Circuit has held that anticipation requires that each and every element of the claimed invention be disclosed in a single prior art reference. Verdegaal Bros. v. Union Oil Co. of California, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Those elements must either be inherent or expressly disclosed and must be arranged as in the claim. In re Bond, 15 USPQ2d 1566 (Fed. Cir. 1990). Additionally, there must be no difference between the claimed invention and the reference disclosed, as viewed by a person of ordinary skill in the art. Richardson v. Suzuki Motor Co., 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

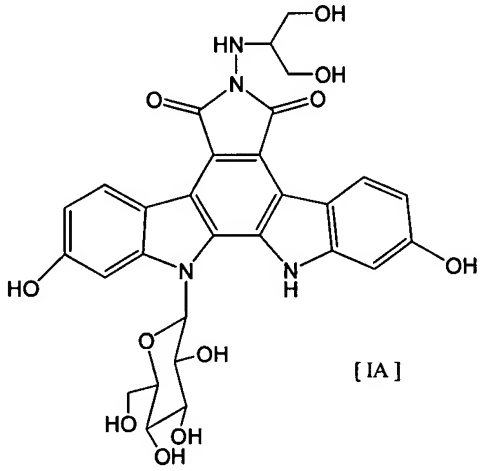
The prior art reference must also be enabling, thereby placing the allegedly disclosed matter in the possession of the public. In re Brown, 329 F.2d 1006, 1011, 241 USPQ 245, 249 (C.C.P.A. 1964). In order to accomplish this, the reference must be so particular and definite that from it alone, without experiment or the exertion of his own inventive skill, any person versed in the art to which it pertains could construct and use it. Id. at 250.

Finally, the Federal Circuit has made it clear that a negative pregnant is not enough to show anticipation. Rowe v. Dror, 112 F.3d 473, 42 USPQ2d 1550 (Fed. Cir. 1997). Thus, where a reference does not explicitly describe anything inconsistent with a claimed use, if that reference nevertheless fails to make

an affirmative suggestion of the claimed limitation, that reference cannot anticipate the claimed use. Id.

Even if the prior art device performs all the functions recited in the claim, the prior art cannot anticipate the claim if there is a structural difference. In re Robertson, 49 USPQ2d 1949, 1951 (Fed. Cir. 1999).

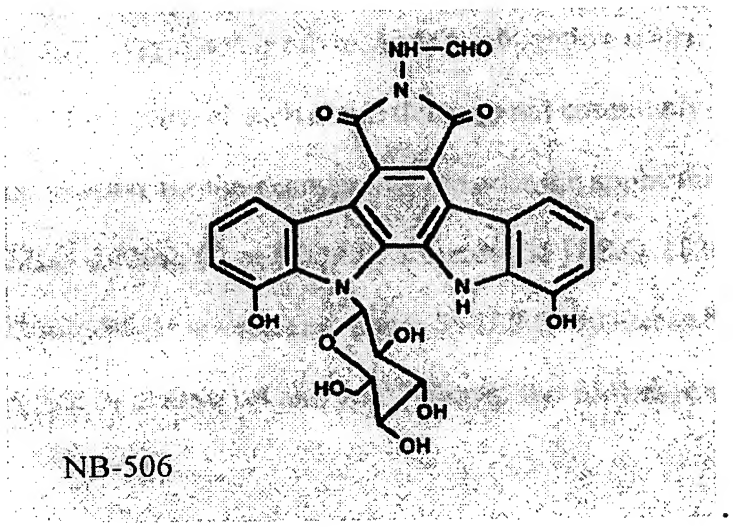
As amended herein, claims 1 and 14 are directed to a preparation for administration in the treatment of cancer and a method for cancer treatment, both of which recite a specific compound of formula IA:



[IA]

in combination with specifically identified antitumor agents.

In contrast, Fukuda, et al. is specifically limited to a combination of the indolocarbazole 6-*N*-formylamino-12,13-dihydro-1,11-dihydroxy-13-(β-D-glucopyranosyl)-5*H*-indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7(6*H*)-dione (NB-506):



The reference specifically notes "The indolocarbazole structure of NB-506 is unique among potent topoisomerase inhibitors" and, as such, the reference is limited to that structure and cannot be said to teach the structure of Applicants' formula IA as recited in amended claims 1 and 14 herein.

Furthermore, Fukuda, et al., is also specifically directed to the combination of NB-506 with cisplatin (CDDP)and camptothecin (CPT-11) and an active metabolite of CPT, SN-38. There is no teaching in the reference of a combination of the indolocarbazole of Applicants' formula IA with an antitumor agent selected from the group consisting of 5-fluorouracil, doxorubicin, etoposide, cisplatin, carboplatin, irinotecan, topotecan and campthotecin, with the possible inclusion, in accordance with the proviso of 5-fluorouracil being present, of leucovorin.

Accordingly, Applicants respectfully submit that the

rejection of claims 1 and 14 under 35 U.S.C. §102(b) as anticipated by Fukuda, et al., is without support in the reference and should be withdrawn.

Claim Rejections 35 USC §103

Claims 1-23 and 34-35 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Fukuda, et al. as applied to claims 1-4 and 14-17 above, and further in view of Kojiri, et al., U.S. 5,922,860. The office action states:

> "The claims of the instant application are drawn to combinations of an indolocarbazole of formula I and an additional anticancer agent, such as cisplatin.
>
> Fukuda et al. disclose synergistic combinations of NB-506 and cisplatin (see abstract-discussion on page 791). Fukuda et al. state that the combination of cisplatin and a topoisomerase I inhibitor has a very interesting strategy for cancer chemotherapy (discussion). What is not taught is the specific compound of formula Ia.
>
> Kojiri et al. teach that compounds having the same formula as those of formula Ia of the instant application and their use as antitumor agents.
>
> It would have been obvious to one of ordinary skill in the art at the time of the invention to use the topoisomerase I inhibitors of Kojiri et al. in combination with cisplatin with these references before them. Fukuda et al. discuss the potential for synergism in cancer therapy when using cisplatin and a topoisomerase I inhibitor. Morover, it is noted that the compounds of formula Ia are very structurally similar to NB-506. It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in the prior art. ***In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069,***

1072 (CCPA 1980). (Claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be prima facie obvious). See also ***In re Crockett, 279 F.2d 274, 126 USPQ 186 (CCPA 1960)*** (Claims directed to a method and material for treating cast iron using a mixture comprising calcium carbide and magnesium oxide were held unpatentable over prior art disclosures that the aforementioned components individually promote the formation of a nodular structure in cast iron.); and ***Ex parte Quadranti, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992)*** (mixture of two known herbicides held prima facie obvious). Thus it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the art disclosed indolocarbazole of Kojiri et al. with another antitumor agent, especially in light of the synergistic effects shown by Fukuda et al. One would have been motivated to combine these agents to form a new composition which would be used for the very same purpose, as an antitumor agent. Moreover, it is noted that the KSR decision forecloses the decision that teaching/suggestion/motivation is required in making an obviousness rejection."

With regard to the now cancelled claims 2-10, 13, 15-23 and 35, Applicants respectfully submit that the present rejection is now moot.

As to amended claims 1, 11-12, 14 and 34, Applicants respectfully traverse the rejection because the prima *facie case* of obviousness has not been established.

The Federal Circuit has ruled that a *prima facie* case of obviousness must establish: (1) some suggestion or motivation to modify the references; (2) a reasonable expectation of success; and (3) that the prior art references teach or suggest all claim limitations. Amgen, Inc. v. Chugai Pharm. Co., 18 USPQ2d 1016, 1023 (Feb. Cir. 1991); In re Fine, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988); In re Wilson, 165 USPQ 494, 496 (C.C.P.A. 1970).

A *prima facie* case of obviousness must also include a showing of the reasons why it would be obvious to modify the references to produce the present invention. See Ex parte Clapp, 277 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). The examiner bears the initial burden to provide some convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings. Id. at 974.

Applicants respectfully submit that a *prima facie* case of obviousness has not been established as there is no convincing line of reasoning which would lead one of ordinary skill in the art to apply only the teachings of Kojiri, et al., to Fukuda, et al. to obtain a synergistic effect between the compound of formula IA and other antitumor agents.

Applicants respectfully submit that, as pointed out in connection with the rejection under 35 U.S.C. §102(b), Fukuda, et al., is limited to a disclosure of a combination of NB-506 with cisplatin or CPT-11 and the effect on human small cell lung cancer cells. As such, the study presented by Fukuda, et al., demonstrates synergistic effect of cisplatin (CDDP) combined only with CPT-11, SN-38, an active metabolite of CPT-11 and NB-506, while noting that combinations do not always enhance antitumor effect: "However, CPT-11 did not always enhance the antitumor effect of CDDP significantly in mice *in vivo* (25, 26)." (Page 791, lines 22-24). Furthermore, Fukuda, et al., only guesses that "CDDP and topoisomerase I inhibitor combinations have

synergistic effects." (Page 791, lines 26-28). Applicants respectfully submit that a "guess" hardly rises to the level of a suggestion much less a teaching.

Applicants further point out that Fukuda, et al., only disclose the indolocarbazole NB-506 in combination with CDDP and CPT-11. Furthermore, the fact that Kojiri, et al., teach an indolpyrrolocarbazole derivative including the compound IA as being a useful antitumor agent does not imply an expectation of suitability in combination with or as exhibiting a synergistic effect when combined with other antitumor agents.

As is very clear, the chemical structures of NB-506 and formula IA are very different. NB-506 has a moiety of -NH-CHO whereas the compound of formula IA has a moiety of -NH-$CH(CH_2OH)_2$. Furthermore, the two OH groups of NB-506 are located at the 1 and 11 positions while those of formula IA are at the 2 and 10 positions. Given these differences in structure, it would not be expected that the properties and reactivity of NB-506 would be readily attributable to the compound of formula IA. In fact, the chemical and structural differences between NB-506 and the compound of formula IA would lead one to expect different properties and reactivity on the part of formula IA than that shown by NB-506 from the teaching of Fukuda, et al., particularly in view of the uncertainty expressed by Fukuda, et al.

Accordingly, Applicants respectfully submit that in view of such differences, one of ordinary skill in the art would not have

expected the specific compound of formula IA to exhibit a synergistic effect in combination with other types of anticancer agents in the manner recited in the claims as amended herein.

Furthermore, as described in the specification of the instant application, the claimed combinations have been shown to exhibit synergistic effects not expected from the teaching of Fukuda, et al. Thus, Table 1 of the specification shows that the compound of formula IA exhibits synergistic antitumor effects when combined with cisplatin, campthotecin, adriamycin (doxorubicin) or carboplatin. Similarly, Table 2 of the specification shows that the compound of formula IA exhibits synergistic antitumor effects when combined with cisplatin, adriamycin doxorubicin) or etoposide.

Looking at Fig. 3 of the present application it is seen that significant inhibition of tumor growth is generated by the combined use of the compound of formula IA and 5-fluorouracil with leucovorin while Tables 5 and 6 show that the combined use of the compound of formula IA with adriamycin (doxorubicin) can significantly decrease the amount of each drug required for effective treatment thereby reducing the exhibition of unwanted side effects.

Neither Kojiri, et al., nor Fukuda, et al., teach or suggest such combinations and the possibility of synergistic effect, least of all the reduced side effects when combined with such antitumor agents as doxorubicin. Such effects are considered

unexpected to one of ordinary skill in the art.

Accordingly, Applicants respectfully submit that the claims as amended herein are not obvious over the cited references and that the rejection under 35 U.S.C. §103(a) has been overcome and should be withdrawn.

In view of the foregoing, Applicants respectfully submit that the present grounds of rejection are either without support or have been overcome and should be withdrawn and that claims 1, 11, 12, 14 and 34 as amended herein are allowable over the prior art.

An early notice of allowance is respectfully requested.

Respectfully submitted,

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H. Jay Spiegel
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